REMARKS

Claims 1 – 6, 8, 9, 11, 24, 27, 29, 30, 33, and 34, as amended, and new claims 40 and 41 are pending in the application. Claims 7, 12 – 23, 25, 26, 28, 31, 32, and 35 – 39 are canceled without prejudice. Claim 1 is amended to incorporate the limitations of claims 7 and 31. Claims 41 and 42 further limit claims 1 and 2 respectively by specifying that the disintegrant is sodium starch glycolate, the disintegrant present in the composition described in the Table of paragraph [0045]. Therefore, no new matter is presented.

Claim 34 stands rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner points out that claim 34 recites two different formulations; one formulation produced by a granulation method and another produced by a direct compression method. In reply, applicants have amended claim 34 to substitute the original table with a new table that clearly sets forth a description of only one formulation made by a granulation method. Applicants submit that with the present amendment to claim 34 the rejection under 35 U.S.C. 112, second paragraph should be reconsidered and withdrawn.

Claims 1 – 9, 11, 24, and 27 – 32 stand rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Application No. 2005/0215528 ("Furuya"). Regarding now-canceled claims 7, 28, 31, and 32, this rejection is deemed to be moot. Regarding claims 1 – 6, 8, 9, 11, 24, 27, 29, and 30, this rejection is respectfully traversed.

Furuya teaches a pharmaceutical composition for preventing or treating a series of diseases such as breast cancer, menopausal syndrome, precocious puberty, etc., wherein the composition is a combination of a GnRH agonist and one of a number of second active ingredients including a SERM, SARM, sex hormone synthesis inhibitor, receptor-type tyrosine kinase inhibitor, bone metabolism modifier, immunotherapeutic drug, cytokine/chemokine inhibitor or an endothelin receptor antagonist. Furuya discloses thousands of potential active ingredients that can potentially be combined with a GnRH agonist to prevent or treat a series of diseases such as breast cancer, menopausal syndrome, precocious puberty, etc. Furuya also discloses numerous

general methodologies and known excipients used in making pharmaceutical formulations. The result is that there are literally millions of combinations of ingredients that can be combined with a required GnRH agonist.

Furuya does not teach or suggest a solid drug formulation comprising granulates containing 30 to 90 mg of ospemifene as the sole active ingredient, in combination with one or more intra-granular excipients, wherein at least one intra-granular excipient is a disintegrant, wherein at least 80% of the formulation is dissolved within 30 minutes after subjecting said formulation to dissolution testing at pH 9.8 according to the USP 24 paddle method.

Applicants respectfully submit that the Examiner has broken the invention into its component parts and found a reference corresponding to many (but not all) of the claim limitations, but failed to provide the necessary suggestion or motivation, before the invention itself, to make the new formulation.

The "as a whole" instruction in title 35 prevents evaluation of the invention part by part. Without this important requirement, an obviousness assessment might successfully break an invention into its component parts, then find a prior art reference corresponding to each component. This line of reasoning would impart hindsight into the obviousness determination by using the invention as a roadmap to find its prior art components. Further, this improper method would discount the value of combining various existing features or principles in a new way to achieve a new result – often the essence of invention.

Contrary to this reasoning, section 103 requires assessment of the invention as a whole. This "as a whole" assessment of the invention requires a showing that an artisan of ordinary skill in the art at the time of the invention, confronted by the same problems as the inventor and with no knowledge of the claimed invention, would have selected the various elements from the prior art and combined them in the claimed manner.

As the Federal Circuit explained in *Ortho-McNeil Pharmaceutical Inc. v. Mylan Laboratories Inc.,* 86 USPQ 2d 1196 (Fed. Cir. 2008), a flexible teaching, suggestion, or motivation (TSM) test remains the primary guarantor against a non-statutory hindsight

analysis, such as is occurring in this case. The alleged teachings of Furuya are noteworthy for what they lack. For example, Furuya provides:

- no working examples except for one drug combination of luprorelin acetate and raloxifene;
- no disclosure relating to dissolution characteristics of the listed drugs; and
- no mention of ospemifene being a preferred embodiment or of the superior profile imparted by granulating ospemifene with an intragranular disintegrant.
- no formulations where a SERM, much less ospemifene, is the sole active ingredient.

In addition, there is no finite, and in the context of the art, small or easily traversed, number of options that would convince an ordinary skilled artisan of obviousness. Therefore, it is improper that the Examiner use an obvious-to-try analysis in this case to support an obviousness allegation.

A finding of obviousness requires that the prior art both suggest the invention and provide one of ordinary skill with a reasonable expectation of success. *In re O'Farrell* 853 F.2d 894, 903, 7 USPQ2d 1673 (Fed. Cir. 1988). Secondary considerations such as unexpected results must be considered if present. *Stratoflex, Inc. v. Aeroquip Corp.,* 713 F.2d 1530, 1538-39, 218 USPQ 871, 879 (Fed. Cir. 1983); *In re Merck & Co., Inc.,* 800 F.2d 1091, 1096, 231 USPQ 375, 378 (Fed. Cir. 1986). In this case, Applicants' claimed formulation, as amended, is not suggested by the prior art and achieves unexpected results.

Assuming for the sake of argument that the Examiner could provide objective evidence of motivation to select ospemifene, granulate the drug with at least one intragranular excipient comprising a disintegrant, the invention possesses unexpected results. Applicants' unexpected results lie in the discovery that the claimed formulation possesses a far superior *in vitro* dissolution profile over tablets of ospemifene made by direct compression techniques. As seen in Figure 1 in the specification, the particular granulated formulation claimed herein shows greater than 80% dissolution in the particular *in vitro* dissolution tests and substantially complete dissolution within two hours. In contrast the ospemifene tablets made by direct compression show approximately 60% dissolution at the thirty minute mark and no more than 80%

dissolution at the two hour time point. Furuya does not motivate the skilled artisan to make granulate formulations of ospemifene wherein at least 80% of the formulation is dissolved within 30 minutes after subjecting said formulation to dissolution testing at pH 9.8 according to the USP 24 paddle method. There is no teaching or suggestion in Furuya to assist the skilled artisan in making an ospemifene formulation having an improved dissolution profile.

Applicants maintain that the Examiner's reliance on *In re Aller* is inapposite. The Examiner cites *In re Aller*, 220 F.2d 454, 456; 105 USPQ 233, 235 (CCPA 1955) for the proposition that where general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. For example, in *Heller* the prior art disclosed a process for decomposing isopropyl benzene hydroperoxide and provided a working example where the process was conducted at a temperature of 100º C and with a 10% sulphuric acid solution. The appellants attempted to claim an identical process except that the temperatures were lower and the sulphuric acid concentrations were higher than the prior art reference. However, the appellants did not appear to show actual improved results over the prior art reference (phenol yields 83.7% v. 75%; 71% v. 60% acetone yields, although prior art silent; reaction times of 20 min to 3 hours v. 1.5 hour reaction times).

The CCPA stated that "[n]ormally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. Under some circumstances, however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art." *Aller* at p. 235.

First, with regard to *Aller*, it should be noted that with "such 'rules of patentability' (and the ever-lengthening list of exceptions which they engender) is that they tend to becloud the ultimate legal issue – obviousness – and exalt the formal exercise of squeezing new factual situations into pre-established pigeonholes. Additionally, the emphasis upon routine experimentation is contrary to the last sentence of section 103." *In re Yates*, 663 F.2d 1054, 1056 (CCPA 1981).

Second, the facts differ from the instant case. Applicants are not simply changing the temperature of a process and the concentration of one of the reaction conditions to obtain an insignificant process improvement. As noted above, the cited prior art, Furuya, discloses thousands of active ingredients and large generic disclosures of pharmaceutical excipients to solve a different problem, e.g. improving the preventative or therapeutic effect of a GnRH agonist on various diseases and improving the quality of life of the patient. There is nothing in Furuya disclosing how granulation and the use of intragranular disintegrants can improve the dissolution of an ospemifene formulation containing 30-90 mg of active ingredient. Further, there is nothing in Furuya disclosing that such a formulation would possess *unexpectedly superior in vitro* dissolution characteristics. One must engage in impermissible hindsight reconstruction using Applicants' invention as a guide in order to arrive at the unique composition to solve the problem faced by Applicants and not recognized by the cited prior art.

Applicants submit that the Examiner is engaging in impermissible hindsight reconstruction using applicants' invention as a starting point to arrive at the claimed invention. Furuya lacks a small and easily traversed number of options one may select from to obtain the claimed composition. Furuya is also completely silent regarding how one may make ospemifene compositions with improved dissolution characteristics. Therefore, claims 1 – 6, 8, 9, 11, 24, 27, and 29 – 32 are patentable over Furuya. Applicants respectfully request the rejection under 35 U.S.C. §103(a) be reconsidered and withdrawn.

Claims 1 – 9, 11, 24, and 27 – 34 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Furuya in view of US Application No. 2003/0162761 ("Steiner"). Regarding now-canceled claims 7, 28, 31, and 32, this rejection is deemed to be moot. Regarding claims 1 – 6, 8, 9, 11, 24, 27, 29, and 30, this rejection is respectfully traversed.

Furuya is deficient for the reasons indicated above.

Steiner relates to pharmaceutical compositions comprising androgen receptor targeting agents ("ARTAs") of a specific chemical formula (I) which does not encompass ospemifene. The ARTAs are a specific subclass of selective androgen receptor

modulators ("SARMs"). The compositions are alleged to be useful for male contraception and a number of diseases or conditions including a variety of hormone-related conditions. Steiner also teaches that the compositions can include a second active ingredient including an LHRH analog, an antiestrogen, an anticancer drug, a 5-alpha reductase inhibitor, an aromatase inhibitor, a progestin, an agent active through other nuclear hormone receptors, a SERM, progesterone, estrogen, a PDE5 inhibitor, apomorphine, a bisphosphonate, or an additional SARM. See paragraph [0121]. Steiner does specifically name any member of the SERM class, much less ospemifene. Further, Steiner provides no working examples of a pharmaceutical formulation containing a SERM and only a generic teaching of the possible formulations one may try including oral (solid or liquid preparations), injection (intravenous, intraarterial, intramuscular), topical, suppository, subcutaneous implantation, and intravaginal formulations. The active compound can also be administered in a vesicle. See paragraphs [0076] to [0080]. Steiner also provides a laundry list of possible excipients one may employ including various binders, disintegrants, plasticizers, buffers, stabilizers, preservatives, and the like.

Steiner does not teach or suggest a solid drug formulation comprising granulates containing 30 to 90 mg of ospemifene as the sole active ingredient, in combination with one or more intra-granular excipients, wherein at least one intra-granular excipient is a disintegrant, wherein at least 80% of the formulation is dissolved within 30 minutes after subjecting said formulation to dissolution testing at pH 9.8 according to the USP 24 paddle method. The skilled artisan at the time of the invention, confronted by the same problems as the inventor and with no knowledge of the claimed invention, would not have been let by Steiner to select the various elements from the prior art and combined them in the claimed manner. Therefore, Steiner is deficient in teaching or suggesting the claimed invention.

Since Steiner is deficient in the same way as Furuya, the combination of Furuya and Steiner is likewise deficient. Therefore, applicants respectfully request that the rejection of claims 1 – 9, 11, 24, and 27 – 34 under 35 U.S.C. §103(a) as being unpatentable over Furuya in view of Steiner be recondisdered and withdrawn.

Applicants thank the Examiner for his consideration of these arguments. If the Examiner believes that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at 734-302-6042.

Respectfully submitted,

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